Prevalence of Sensory Neuropathy in Type 2 Diabetic Patients in Iranian Population (Yazd Province)

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ABSTRACT

BACKGROUND: The aim of this study was to determine the prevalence and risk factors of the sensory neuropathy in type 2 diabetic patients referring to Yazd Diabetes Research Center. Neuropathy is one of the most common complications of both type 1 and type 2 diabetes mellitus.

MATERIAL AND METHODS: This is a cross-sectional study on 2350 diabetic patients (1071 male, 1279 female) referred to Yazd Diabetes Research Center (Iran) from June 2007 to February 2008. Data collection was carried out through a questionnaire including demographic subject, duration, body weight and length, lab test (HbA1c, 2hpp, FBS), Body Mass Index (BMI). Blood Pressure was measured on the right arm after a five-min rest. Neuropathy was confirmed using a Semmes Weinstein 10 g monofilament over 10 areas of the feet, ankle reflexes and vibration over the great toe and ankle.

RESULTS: The prevalence of type 2 diabetes and diabetic sensory neuropathy in Yazd province is 14.5% and 51.7%, respectively. The prevalence of sensory neuropathy in male was 49.9% and 53.2 % in female, that increased by age ($P = 0.001$), duration of diabetes ($P = 0.001$), HbA1c ($P = 0.001$) and poor glycemic control (high FBS and 2hpp).

CONCLUSION**:** Age, duration of diabetes, HbA1c and poor glycemic control were considered to be the risk factors for sensory neuropathy

KEY WORDS: Type 2 diabetes mellitus, prevalence, sensory neuropathy.

INTRODUCTION

The prevalence of type 2 diabetes mellitus at the age of 30 years and above was evaluated as 14.2% in Yazd that is the highest prevalence of diabetes in Iran (1). For many patients, diabetes mellitus would be little more than a troublesome but manageable metabolic disorder were it not for its devastating late complications. Diabetes mellitus is the leading cause of peripheral neuropathy. Peripheral neuropathy affects at least 15% of all patients with diabetes (2) and 37% of patients aged 18 years and older with insulin-dependent diabetes mellitus. The prevalence of neuropathy depends on the specific definition used (3). Diabetic neuropathy is a distal symmetric sensor motor polyneuropathy that is the most common type (75% of all) (4), sometimes complicated by focal neuropathies such as median nerve entrapment or other mononeuropathies, polyradiculopathies, or autonomic neuropathy (2). The development of clinical diabetic polyneuropathy is defined by the presence of detectable sensory, motor, or

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autonomic deficits on clinical examination, with or without the presence of dysesthetic or paresthetic symptoms (5). Clinical neuropathy is the progressive damage and loss of nerve fibers and is detectable by nerve conduction and autonomic nervous system tests (6). Advanced distal sensorimotor and autonomic deficits cause most foot ulcers and amputations in patients with diabetes (4). Although the frequency of diabetic neuropathy increases with the duration and severity of antecedent hyperglycemia (3, 7), the ability of metabolic intervention to prevent or ameliorate clinical neuropathy has not been convincingly established. Diabetic neuropathy remains untreatable except by palliative measures.

MATERIAL AND METHODS

This is a cross-sectional study performed on 2350 diabetic patients (1071 male, 1279 female) referred to Yazd Diabetes Research Center Iran from June 2007 to February 2008. The selected patients were evaluated for sensory vascular disease and neuropathy. Each person underwent a detailed historical and complete clinical examination. Details regarding demographic subject, duration of diabetes, body weight and height were recorded in all patients. Height without shoes and weight were measured. Body Mass Index (BMI) was calculated as kilograms divided by the square of height in meters. Blood glucose level estimation was done by colorimetric method in venous blood (in WL 546 nm). Glycated hemoglobin (HbA1c) was measured by HPLC method using DS5 analyzer. Blood pressure was measured on the right arm supported on the table at heart level after a five-min rest. Hypertension was diagnosed according to WHO criteria (systolic blood pressure>140 mmHg or diastolic blood pressure >90 mmHg). Sensory neuropathy was assessed by any past experience of numbness, paresthesis, and tingling, burning sensation. Then neuropathy was confirmed using a Semmes-Weinstein 10g monofilament over 10 areas of the feet, ankle reflexes and vibration over the great toe and ankle. Neuropathy was confirmed if there were at least three areas on each foot with loss of sensation over the great toe and ankle. Painful peripheral neuropathy was diagnosed using any record of pain worsening at night.

All statistical analyses were performed using SPSS 11.5 for Windows and kappa and paired test. Data of continuous variables were expressed as mean ± standard deviation. Differences between groups were assessed by the paired sample tests. Statistical significance was set at $P < 0.05$.

RESULTS

Of the initial sample, 2350 patients (1071 male, 1279 female) completed the study. 680 of female patients (53.2%) and 534 of male patients (49.9%) had peripheral neuropathy. The prevalence of type 2 diabetes and diabetic neuropathy in Yazd province was evaluated 14.5% and 51.7%, respectively. The mean age of patients was 55.93 ± 10.08 years, mean duration of diabetes 11.75 ± 6.85 years, mean of Fasting Blood Sugar (FBS) 11.03 ± 3.93 mmol/l and mean of 2 hour post prandial (2hpp) was 17.06 ± 5.09 mmol/l. The mean of HbA1c was 9.94 ± 2.21, mean of SBP 132.00 ± 19.86 and DBP 80.50 ± 6.57 (Table 1).

Table 1- Characteristic of type 2 diabetic subjects in the study

Subject characteristic		Result
Demographic characteristic	Means Age (years)	55.93 (R: 26-80)
	Sex: Female/Male	1.1942
Clinical	Mean diabetes duration (years)	11.75 (R: 1-34)
	FBS (mmol/l, mean ± SD)	11.030 ± 3.9278
	2HPP (mmol/l, mean ± SD)	17.062 ± 5.093
	BMI (kg/m2, mean ± SD)	27.77 ± 4.24
	HbA1c (%, mean ± SD)	9.94 ± 2.21
	DBP (mmHg, mean ± SD)	80.50 ± 6.57
	SBP (mmHg, mean ± SD)	132.00 ± 19.86

FBS: Fasting blood sugar**; 2hpp:** 2hour postprandial**; BMI**: Body Mass Index**; HbA1c:** Glycated hemoglobin**;**
DBP: Diastolic Blood Pressure**; SBP:** Systolic Blood Pressure.

The prevalence of neuropathy in patient between 26 to 39 years was 44.6% and in patients with the age of 40 to 54 years was 49.9% and patients with range of age between 55 to 69 years was 50.6% and above 70 was 66.5%. The prevalence of neuropathy increased by age (P = 0.001), (Table 2). The prevalence of neuropathy in patient with BMI under 20 kg/m2 was 66.7% and in patient with BMI 20 till 24.9 kg/m2 was 49.9% and patient with range of BMI 25 till 29.9 was 47.5% and above 30 was 60.5%. There was no statistically significant increase in BMI (P = 0.352) (Table 2).

The prevalence of sensory neuropathy increased by duration of diabetes (P = 0.001) and HbA1c (P = 0.001). There was a statistically significant difference between increase of DBP and neuropathy (P = 0.041). Age, duration of diabetes, HbA1c and poor glycemic control (high FBS and 2Hpp) were considered to be the risk factors for neuropathy (Table 2).

Table 2- Multivariate analysis of risk factors affecting the prevalence of diabetic neuropathy

Subject characteristic		**Neuropathy**		***P* value**
		n	**DN (%)**	
Age	(26-39 years)	121	54 (44.6)	0.001
	(40-54)	967	483(49.9)	
	(55-69)	1023	518 (50.6)	
	(70-80)	239	159 (66.5)	
Sex	male	1071	534 (49.9)	0.06
	female	1279	680 (53.2)	
BMI kg/m^2	(<20)	30	20 (66.7)	0.352
	(20.1-24.9)	618	305 (49.9)	
	(25-29.9)	1073	510 (47.5)	
	(>30)	608	368 (60.5)	
Duration	(<5 yrs)	486	153 (31.7)	0.001
	(5-10)	1297	681 (52.5)	
	(10-15)	309	214 (69.3)	
	(>15)	261	166 (63.6)	
FBS (mg/dl)	Good (<100)	143	70 (49.0)	0.249
	Fair (100-119)	197	112 (56.9)	
	Poor (120-199)	869	370 (42.9)	
	Very poor (>200)	1147	662 (57.7)	
2hpp (mg/dl)	Good (<140)	38	17 (44.7)	0.041
	Fair (140-199)	276	107 (38.8)	
	Poor (200-249)	390	199 (51.0)	
	Very poor (>250)	1646	891 (54.1)	
HbA1c (%)	Good (<7.5)	334	139 (41.6)	0.001
	Fair (7.5-7.99)	81	55 (69.7)	
	Poor (8-9.49)	676	351 (51.9)	
	Very poor (>9.5)	1259	669 (53.1)	
DBP (mmHg)	Good (<80)	421	236 (56.1)	0.001
	Fair (80-89)	1387	657(47.4)	
	Poor (90-99)	536	315(58.8)	
	Very poor (>10)	6	6(100)	
SBP (mmHg)	Good (<120)	431	220 (51.0)	0.249
	Fair (120-139)	1028	499 (48.5)	
	Poor (140-159)	553	323 (58.4)	
	Very poor (>160)	338	172 (50.9)	

DISCUSSION

In the current study we found out that the prevalence of neuropathy was 51.7% which increased by age. Prevalence of neuropathy was very high in patients aged above 70 years (66.5%). The prevalence of diabetic neuropathy has been reported in unselected diabetes from less than 5 to approximately 60 per cent**.** This variability was due to differences in age, sex, duration of diabetes, type of diabetes and criteria of diagnosis. The most frequent forms of diabetic neuropathy are the distal symmetric sensorimotor and the autonomic neuropathy which affect nearly 90% of patients with diabetic neuropathy (19).

Duration of diabetes and HbA1c were major risk factors for diabetic sensory neuropathy in our study. Elucidating the risk factors for neuropathy is important, given the association between the risk factors and increased diabetes-related morbidity and mortality (20). Mortality in patients with neuropathy is high, and the cause of death is often coronary heart disease (23,24). Previous cross-sectional studies have reported associations between neuropathy and body height (25), cigarette smoking (26), low levels of HDL cholesterol (27) and hypertension (27, 28) in addition to established risk factors, level of glycemia and duration of diabetes.

Mean of DBP was 80.50± 6.57 in our study and increase in DBP was found to be an important factor for diabetic neuropathy. Hypertension was observed to be a strong risk factor for diabetic neuropathy in 463 young patients (29). A follow-up of patients with either type 1 or type 2 diabetes suggested that both type 1 and type 2 diabetes and markers of microvascular disease are associated with the severity of neuropathy (30).

The baseline cross-sectional data in the present study (31) are evidence of association between neuropathy and microvascular complications, suggesting a common pathogenic mechanism (32,33 and 34).

Fasting Blood Sugar and 2 hour postprandial had important role in diabetic neuropathy in our analysis. Triglyceride level and obesity were strong predictors of microalbuminuria and retinopathy in type 1 diabetic patient (35,36). A relation between insulin resistance and microvascular complications including neuropathy is associated with endothelial dysfunction (37). Other complications of diabetes linked to endothelial dysfunction may also have the risk of microalbuminuria, retinopathy and neuropathy (35,36).The pathogenetic mechanisms responsible for the progressive loss and damage of nerve fiber underlying clinical diabetic polyneuropathy (15) remain controversial and may involve direct metabolic and microvascular ischemic insult (17).

Hyperglycemia or other metabolic consequences of insulin deficiency in both components of this disease process, strongly implicate abundant clinical, animal and in vitro data (17, 18). Thus, the salutary effects of intensive diabetes therapy aimed at achieving normal glucose levels on peripheral nerve function in patients with insulin-dependent diabetes mellitus were first recognized by Gregersen (19) before 1990, has a firm scientific underpinning. Nevertheless, the clinical benefit of improved metabolic control in preventing or delaying the signs or symptoms of diabetic peripheral polyneuropathy remained unproven, although surrogates for clinical neuropathy such as nerve conduction or vibration perception threshold, had been noted to improve with intensified diabetic therapy (20, 21 and 22).

Estimates of the prevalence of diabetic peripheral neuropathy vary widely in the literature (6, 7). Differences in the diagnostic criteria and the different methods of patient selection cause different prevalence. Whilst some authors have considered painful symptoms alone to be diagnostic (6), others have required signs of nerve dysfunction (8). Dyck et al. (9) proposed that two of the following three criteria should be present for a diagnosis of peripheral neuropathy: signs of peripheral neuropathy, abnormalities of quantitative sensory testing or abnormal electrophysiological tests. Routine out-patient practice and mass screening requirements have led to the development of simpler scoring techniques for both symptoms (10,11 and 12) and signs (13,14).

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REFERENCES

1. Afkhami-Ardekani M, Vahidi S, Vahidi A, Ahmadieh M. The prevalence of type 2 diabetes mellitus on age of 30 years and above in Yazd province (Iranian population). Journal of Shahid Sadoughi University of Medical Sciences and Health Services 2001;9(1):22-27.
2. Dyck PJ, O'Brien PC. Meaningful degrees of prevention or improvement of nerve conduction in controlled clinical trials of diabetic neuropathy. Diabetes Care 1989;12:649-652.
3. Maser RD, Steenkiste AR, Dorman JS, Nielsen VK, Bass EB, Qurasha M, et al. Epidemiological correlates of diabetic neuropathy. Report from Pittsburgh Epidemiology of Diabetes Complications Study. Diabetes 1989;8:1456-1461.
4. Greene D, Sima A, Albers J, Pfeifer M. Diabetic neuropathy. In: Ellenberg M, Rifkin H, Porte D, editors. Diabetes Mellitus: Theory and Practice. Fourth ed. New York: Elsevier; 1990:710-755.
5. Report and recommendation of the San Antonio conference on diabetic neuropathy. Consensus statement. Diabetes 1988;37:1000-1004.
6. Goodman JL, Baumoel S, Frankel L, Marcus LJ, Wasserman S. The diabetic neuropathies. Illinois: CC Thomas Springfield;1953:1-66.
7. Neil HAW, Thompson AV, Thorogood M, Fowler GH, Mann JI. Diabetes in the elderly: the Oxford community diabetes study. Diabetic Med 1989;6:608-613
8. Consensus statement: Report and recommendations of the San Antonio conference on diabetic neuropathy. American Diabetes Association and American Academy of Neurology. Diabetes Care 1988;11:592-597.
9. Dyck PJ, Karnes JL, Daube J, O'Brien R, Service FJ. Clinical and neuropathologic criteria for the diagnosis and staging of diabetic polyneuropathy. Brain 1985;108:861-880.
10. Pirart J. Diabetes mellitus and its degenerative complications: a prospective study of 4400 patients observed between 1947 and 1973. Diabetes Care 1979;1:168-188.
11. Dyck PJ. Detection, characterization and staging of polyneuropathy assessed in diabetics. Muscle Nerve 1988;11:21-32.
12. Masson EA, Gem J, Hunt L, Boulton AJM. A novel approach to the diagnosis and assessment of symptomatic diabetic neuropathy. Pain 1989;38:25-28.
13. Pirart J. Diabetes mellitus and its degenerative complications. A prospective study of 4,400 patients observed between 1947 and 1973. Diabetes Care 1978;1:168-188.
14. Dyck PJ, Kratz KM, Lehman KA. The Rochester diabetic neuropathy study: design, criteria for types of neuropathy, selection bias, and reproducibility of neuropathic tests. Neurology 1991;41:799-807.
15. Franklin GM, Kahn LB, Bacter J, Marshall JA, Hamman RF. Sensory neuropathy in non-insulin dependent diabetes mellitus. The San Luis Valley study. Amer J Epidemiol 1990; 131: 633- 643.
16. Greene DA, Sima AA, Stevens MJ, Feldman EL, Lattimar SA. Complications: neuropathy, pathogenetic considerations. Diabetes Care 1992;15:1902-1925.
17. Committee on Health Care Issues ANA. Does improved control of glycemia prevent or ameliorate diabetic neuropathy? Ann Neurol 1986;19:288-290.
18. The DCCT Research Group. Factors in the development of diabetic neuropathy. Diabetes 1988;37:476-481.
19. Thomas PK, Eliasson SG. Diabetic Neuropathy in Dyck PJ(ed). Peripheral neuropathy. Philadelphia: Sauders; 1984:1773-1810.
20. Greene DA. Metabolic control. In: Dyck PJ, Thomas PK, Asbury AK, Winegrad AI, Porte D, editors. Diabetic Neuropathy. Philadelphia:Saunders;1987:177-187.
21. Reichard P, Nilsson BY, Rosenqvist U. The effect of long-term intensified insulin treatment on the development of microvascular complications of diabetes mellitus. N Engl J Med 1993;329:304-309.
22. Boulton AJ, Worth RC, Drury J, Hardisty CA, Wolf E, Cudworth AG, et al. Genetic and metabolic studies in diabetic neuropathy. Diabetologia 1984;26:15-19.
23. Forsblom CM, Sane T, Groop PH, Tötterman KJ, Kallio M, Saloranta C, et al. Risk factors for mortality in Type II (non-insulin-dependent) diabetes: evidence of a role for neuropathy and a protective effect of HLA-DR4. Diabetologia 1998;41:1253-1262.
24. Coppini DV, Bowtell PA, Weng C, Young PJ, Sonksen PH. Showing neuropathy is related to increased mortality in diabetic patients -- a survival analysis using an ac-

celerated failure time model. J Clin Epidemiol 2000;53:519-523.
25. Gadia MT, Natori N, Ramos LB, Ayyar DR, Skyler JS, Sosenko JM. Influence of height on quantative sensory, nerve-conduction, and clinical indices of diabetic peripheral neuropathy. Diabetes Care 1987;10:613-616.
26. Mitchell BD, Hawthorne VM, Vinik AI. Cigarette smoking and neuropathy in diabetic patients. Diabetes Care 1990;13:434-437.
27. Maser RE, Steenkiste AR, Dorman JS, Nielsen VK, Bass EB, Manjoo Q, et al. Epidemiological correlates of diabetic neuropathy: report from Pittsburgh Epidemiology of Diabetes Complications Study. Diabetes 1989;38:1456-1461.
28. Harris M, Eastman R, Cowie C. Symptoms of sensory neuropathy in adults with NIDDM in the U.S. population. Diabetes Care 1993;16:1446-1452.
29. Forrest KY, Maser RE, Pambianco G, Becker DJ, Orchard TJ. Hypertension as a risk factor for diabetic neuropathy: a prospective study. Diabetes 1997;46:665-670.
30. Dyck PJ, Davies JL, Wilson DM, Service FJ, Melton LJ III, O'Brien PC. Risk factors for severity of diabetic polyneuropathy: intensive longitudinal assessment of the Rochester Diabetic Neuropathy Study cohort. Diabetes Care 1999; 22:1479-1486.
31. Tesfaye S, Stevens LK, Stephenson JM, Fuller JH, Plater M, Ionescu-Tirgoviste C, et al. Prevalence of diabetic peripheral neuropathy and its relation to glycaemic control and potential risk factors: the EURODIAB IDDM Complications Study. Diabetologia 1996; 39:1377-1384.
32. Cameron NE, Eaton SE, Cotter MA, Tesfaye S. Vascular factors and metabolic interactions in the pathogenesis of diabetic neuropathy. Diabetologia 2001;44:1973-1988.
33. Tesfaye S, Harris N, Jakubowski J, Mody C, Wilson RM, Rennie IG, et al. Impaired blood flow and arterio-venous shunting in human diabetic neuropathy: a novel technique of nerve photography and fluorescein angiography. Diabetologia 1993;36:1266-1274.
34. Eaton SE, Harris ND, Ibrahim S, Ibrahim S, Patel KA, Selmi F, et al. Increased sural nerve epineurial blood flow in human subjects with painful diabetic neuropathy. Diabetologia 2003;46:934-939.
35. Chaturvedi N, Sjoelie AK, Porta M, Aldington SJ, Fuller JH, Songini M, et al. Markers of insulin resistance are strong risk factors for retinopathy incidence in type 1 diabetes. Diabetes Care 2001;24:284-289.
36. Chaturvedi N, Bandinelli S, Mangili R, Penno G, Rottiers RE, Fuller JH. Microalbuminuria in type 1 diabetes: rates, risk factors and glycemic threshold. Kidney Int 2001; 60:219-227.
37. Zenere BM, Arcaro G, Saggiani F, Rossi L, Muggeo M, Lechi A. Noninvasive detection of functional alterations of the arterial wall in IDDM patients with and without microalbuminuria. Diabetes Care 1995;18:975-982.